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(54) **HDL-BOOSTING COMBINATION THERAPY COMPLEXES**

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(57) **ABSTRACT**

A pharmaceutical composition including therapeutically effective amounts of at least one HMG-CoA reductase inhibitor present as a dyhydroxyacid salt and at least one additional therapeutic agent.

HDL-BOOSTING COMBINATION THERAPY COMPLEXES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. application Ser. No. 10/983,836, filed Nov. 8, 2004, which claims priority from U.S. Provisional Patent Application No. 60/518,091 filed Nov. 7, 2003. The present invention relates to the use of water-soluble salts of dihydroxy open acid statins that are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in combination with at least one additional therapeutic agent.

BACKGROUND

[0002] Various medical conditions, including but not limited to certain forms of cancer, hepatic malfunctions, dementias such as Alzheimer's disease, and various lipid abnormalities can be advantageously treated using inhibitors of HMG-CoA reductase. It is also posited that various other diseases and medical conditions are related to pathways that utilize HMG-CoA reductase. Thus treatment regimens utilizing HMG-CoA reductase inhibitors are valuable and warranted.

[0003] In many instances, combination therapies employing two or more therapeutic compounds are required to adequately address the medical condition and/or physical effects secondary to the condition under treatment. Thus, HMG-CoA reductase inhibitors can be employed with various other therapeutic agents to address lipid abnormalities. Combining two lipid-lowering medications safely and effectively improves overall beneficial effect on all lipid abnormalities and reduces multiple coronary heart disease risk factors.

[0004] Coronary heart disease (CHD) is currently managed by various drug therapies that include HMG-CoA reductase inhibitors (collectively known as statins), as well as other compounds such as fibrates, bile acid sequestrants, niacin and the like. Of these drugs, statins are the most prescribed because they are effective in lowering total cholesterol and low-density lipoprotein cholesterol (LDL-C). It has been found that statins have a small to moderate effect on triglycerides and a minimal effect at raising high-density lipoprotein cholesterol (HDL-C) levels, the so-called "good cholesterol". While the National Cholesterol Education Program (NCEP) treatment guidelines recognize LDL-C as the primary target of therapy for prevention, it now focuses on HDL-C levels as a major risk factor. Moreover, the Adult Treatment Panel (ATP) of NCEP has now raised the HDL-C lower limit from 35 mg/dL to 40 mg/dL.

[0005] Statins are not effective at increasing HDL-C. However, various other materials such as fibrates can increase the level of HDL-C "good cholesterol." Combined statin and fibrate therapy is often imperative for the improvement of the serum lipid profile in patients with mixed hyperlipidemia. However, the potential risk of myopathy has limited the widespread use of such therapy. Current combination therapies recommend separate dosing to minimize peak dose interactions. Thus, dosing regimens can include weekly administration of a material such as a fibrate together with daily statin treatment. Other treatment regimens may include a fibrate prescribed in the morning and a statin prescribed at night to minimize peak dose interactions. Such dosing complexity can

[0006] Thus, it would be desirable to develop formulations of water-soluble salts of statin dihydroxy open acid and other suitable components having suitable effect on cholesterol, triglyceride, or related blood chemistries. It would also be desirable to provide a formulation of such materials in a single pill or dose form in order to address the overall lipid abnormalities. It would also be desirable to provide a dose form in which the water-soluble statin dihydroxy acid salt and other lipid addressing materials are present in a form that would enable formulation of a combination drug that can be administered at therapeutically effective low doses in order to eliminate undesirable side effects.

[0007] Similar dosing complexities exist in treating other medical conditions for which HMG-CoA reductase inhibitors can be utilized. Thus, it would be desirable to provide therapeutic compositions that combine HMG-CoA reductase inhibitors and other complementary agents in a single dose form for treating various illnesses and conditions that are moderated or controlled by HMG-CoA reductase.

SUMMARY

[0008] Disclosed herein is a therapeutically effective formulation involving a combination of an HMG CoA reductase inhibitor and at least one other therapeutic agent. The combined formulation is designed to improve the overall beneficial effect on all lipid parameters. The combined formulary can consist of a water soluble salt of a dihydroxy open acid statin and a water soluble salt of a fibrate.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0009] Currently used therapeutic agents addressing lipid abnormalities, particularly those occurring in coronary heart disease include, HMG Co-A reductase inhibitors. Other therapeutic agents addressing lipid abnormalities include, but are not limited to, fibrates, bile acid sequestrants, and niacin. Each of these materials is typically administered as monotherapies in which multiple materials are independently administered to address various lipid abnormalities. Disclosed herein is a pharmaceutical formulation in which at least two therapeutically effective entities are combined and can have the effect of reducing factors such as total cholesterol, LDL-C, triglycerides, and/or at increasing levels of HDL-C, popularly known as "good cholesterol".

[0010] In addition to use as therapeutic agents addressing lipid abnormalities, HMG-CoA reductase inhibitors have demonstrated efficacy in the treatment of certain forms of cancer as well as the potential for addressing symptoms of Alzheimer's disease.

[0011] Disclosed herein is a therapeutic combination that contains at least one therapeutically active form of an HMG CoA reductase inhibitor and at least one additional therapeutic agent that is a compound other than an HMG CoA reductase inhibitor. The additional therapeutic agent may be capable of addressing at least one lipid abnormality.

[0012] As defined herein, the term "lipid abnormality" is taken to mean a deviation in at least one of total cholesterol value, LDL-C, triglyceride, or HDL-C levels from that defined as normal or acceptable by the National Cholesterol Education Program. The currently accepted normal values are listed in Table I. It is understood that the materials utilized

number of individuals. Thus, the materials utilized in the therapeutic composition disclosed herein will address at least one of total cholesterol, HDL-C, LDL-C, and triglycerides. It is contemplated that the materials may address more than one of the aforementioned abnormalities as desired or required.

TABLE 1

Normal Serum Values (mg/dL) for Various Lipoprotein Materials as Defined by National Cholesterol Education Program

RATING CATEGORY	LDL CHOL	HDL CHOL	TRIGLYCERIDES	TOTAL CHOLESTEROL
Optimum	<100	>60	<100	—
Near Optimum	100-129	50-59	100-149	<200
Increased Risk	130-159	41-49	150-199	200-239
High Risk	160-189	35-40	200-399	>240
Very High Risk	>190	<35	>400	—

[0013] It is contemplated that "addressing at least one lipid abnormality" will be evidenced by a positive trending resolution toward the desired value as defined by appropriate agencies and individuals. It is to be understood that the material of choice may exhibit effect on lipid and lipid-like materials even within the range defined as acceptable by the appropriate agency or individual and/or that defined in Table I.

[0014] It is contemplated a therapeutic agent capable of addressing at least one lipid abnormality can include at least one of peroxisome proliferator-activated receptor agonists, cholesterol ester transfer protein modifiers, either as inhibitor or agonist, long-chain carboxylic acids, long chain carboxylic ether compounds, and the like. Examples of such materials can include but are not limited to water soluble materials such as fibrates, niacin and insoluble or semisoluble materials such as bile acid sequestrants.

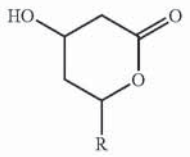
[0015] It is contemplated that the therapeutic agent is used in combination with a suitable HMG CoA reductase inhibitor. The HMG CoA reductase inhibitor in the composition can be present as its biologically active form.

[0016] The term "HMG CoA reductase inhibitor" as used herein is intended to include inhibitors of the 3-hydroxy-3-methylglutaryl co-enzyme A reductase pathways. In particular these include statins: a structural class of compounds that contains a moiety that can exist either as a 3-hydroxy lactone ring, or as the corresponding dihydroxy open acids.

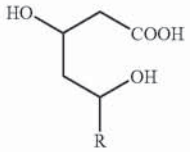
[0017] All hydrates, solvates, and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described dihydroxy open moiety are included within the scope of the term "statin". Pharmaceutically acceptable salts and esters of the dihydroxy open acid statins are included within this term.

[0018] Statins inhibit HMG-CoA reductase in the dihydroxy open acid form. Compounds that have inhibitory activity for HMG-CoA reductase can be readily identified using assays well known in the art. Examples of such assays are described or cited in U.S. Pat. No. 4,231,938 at column 6. As disclosed herein, the HMG-CoA reductase inhibitor can advantageously be a dihydroxy open acid statin.

[0019] The term "dihydroxy open acid statin(s)" is intended to be defined as statins containing the dihydroxy open acid moiety including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin" herein and are all intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates, and polymorphic crystalline forms are encompassed within the scope of the term "dihydroxy open acid statin(s)." In the broadest sense, any dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof may be used in the present invention. The HMG CoA reductase inhibitor can be one derived from the lactone form having the general formula:



in which R is the statin chromophore of the respective compound. The HMG CoA reductase inhibitor compound employed herein is present as its biologically active form having the general formula:



in which R is the statin chromophore for the respective compound. Non-limiting examples of statin chromophores include at least one of simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin. The materials of choice generally exhibit water solubility.

[0020] As used herein "water solubility" is defined as the ability of at least a portion of the material to dissolve or be solubilized by water. Thus, examples of dihydroxy open acid statins that may be used with the present invention include, but are not limited to, dihydroxy open acid forms and pharmaceutically acceptable salts and esters of materials such as: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, pitavastatin, rosuvastatin.

[0021] In the broadest sense, pharmaceutically acceptable salts of statin dihydroxy-acid include, but are not limited to, cation salts such as sodium, potassium, aluminum, calcium,

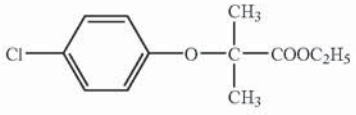
ylene diamine, n-methylglucamine, lysine, arginine, ornithine, choline, N—N' dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p chlorobenzyl-2 pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2 pentamine, and tris(hydroxylmethyl) aminomethane, as well as pharmaceutically acceptable esters to include, but not be limited to, C_{1-4} alkyl and C_{1-4} alkyl substituted with phenyl, dimethylamino, and acetylamino. As used herein, the term "C_{1-4}alkyl" includes straight or branched aliphatic chains containing from one to four carbon atoms. Nonlimiting examples include straight or branched aliphatic chains such as, methyl, ethyl, n-propyl, n-butyl, iso-propyl, sec-butyl and tert-butyl.

[0022] It is contemplated that the dihydroxy open acid statin will be formulated for oral administration in a manner that allows for delivery of the dihydroxy open acid statin without its lactone counterpart. As desired or required, the dihydroxy open acid statin can be formulated to be delivered directly to the absorptive mucosa of the small intestine, thus allowing for absorption of the open acid statin into portal circulation, penetration by the open active statin into hepatocytes to achieve enhanced efficacy and systemic exposure consisting of open acid moieties. Without being bound to any theory, it is believed that maintaining the statin in its open acid form in the body reduces the potential for drug interactions between statins (whose metabolism is CYP3A4-mediated) and other active agents (that inhibit this CYP3A4 enzymatic pathway), thereby providing enhanced efficacy of the composition disclosed herein.

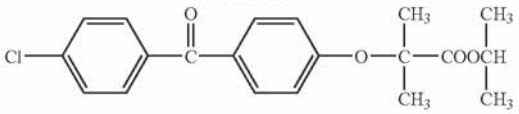
[0023] As disclosed herein, the pharmaceutical composition also includes at least one additional material exhibiting at least one anti-hypercholesterolemic effect. The material of choice can be lipid lowering compounds or agents having other pharmaceutical activities, or agents having both lipid lowering effects and other pharmaceutical activities. Suitable materials will be preferably water-soluble. Nonlimiting examples of additional active agents that can be advantageously employed in the formulation disclosed herein will be water soluble and can include HMG-CoA reductase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A, cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2, as well as dual inhibitors of ACAT-1 and ACAT-2, microsomal triglyceride transfer protein (MTP) inhibitors, probucol, niacin, cholesterol absorption inhibitors such as SCH-58235, also known as ezetimibe and 1-(4-fluorophenyl)-3(R)-3(S)-(4-fluorophenyl)-3-hydroxypropyl), 4(S)-4-hydroxyphenol (−2-azetidinone) described in U.S. Pat. Nos. 5,727,115 and 5,846,966, bile acid sequestrants, LDL, (low density lipoprotein) receptor inducers, platelet aggregation inhibitors (for example glycoprotein IIb/IIa fibrinogen receptor antagonists and aspirin. Human peroxisome proliferator activated receptor gamma (PPARγ) agonists may also be employed including the compounds commonly referred to as glitazones, for example troglitazone, pioglitazone, and rosiglitazone, and those compounds included within the structural class known as thiazolidinediones, as well as those PPARγ agonists outside the thiazolidinedione structure class, PPARα agonists such as clofibrate, fenofibrate, gemfibrozil, bezafibrate, and ciprofibrate, PPAR dual α/γ agonists, vitamin B_6 (also known such as sodium salt and the methylglucamine salt, anti-oxidant vitamins such as vitamin C and E and beta-carotene, beta-blockers, angiotensin II antagonists such as losartan, angiotensin converting enzyme inhibitors such as enalapril and captopril, calcium channel blockers such as nifedipine and diltiazem, endothelial antagonists, and the like. Other non-limiting examples of water soluble therapeutic agents include compounds associated with anti-retroviral therapies such as those employed in the treatment of AIDS infected patients to treat lipid abnormalities associated with such treatment. These may include HIV protease inhibitors such as indinavir, nelfinavir, ritinavir and saquinavir.

[0024] More particularly, it is contemplated that the therapeutic agent used in connection with the dihydroxy open acid salt of the suitable statin will include at least one of fibrates, bile acid sequestrants, and nicotinic acid or niacin. As used herein, "fibrates" refer to a class of lipid lowering drugs used to treat various forms of hyperlipidemia (elevated serum triglycerides) that may be associated with hypercholesterolemia. The fibrates of choice are water-soluble compounds having the effect of treating people with very high triglyceride levels through the lipoprotein lipase-mediated effect on lipolysis and by reducing triglyceride production in the liver. The fibrates of choice may also increase HDL-C by regulating apolipoprotein (apo)AI and (apo)AII gene expression. The fibrates of choice, in addition to alterations in plasma HDL-C levels, can induce emergence of large, cholesteryl ester-rich HDL. Fibrates can be defined as PPAR-alpha agonists (peroxisome proliferator activated receptor alpha agonists), including fibric acid derivatives and pharmaceutically acceptable salts and esters of such fibric acid derivatives, such as clofibrate, the ethyl ester of p-chlorophenoxyisobutyrate. Fibric acid derivatives lower the levels of triglyceride-rich lipoproteins, such as VLDL, raise HDL levels, and have variable effects on LDL levels. The effects on VLDL levels appear to result primarily from an increase in lipoprotein lipase activity, especially in muscle. This leads to enhanced hydrolysis of VLDL triglyceride content and an enhanced VLDL catabolism. Fibric acid agents also may alter the composition of the VLDL, for example, by decreasing hepatic production of apoC-III, an inhibitor of lipoprotein lipase activity. These compounds are also reported to decrease hepatic VLDL triglyceride synthesis, possibly by inhibiting fatty acid synthesis and by promoting fatty acid oxidation as a result of peroxisomal proliferation.

[0025] Fibrate derivatives include but are not limited to the salts of clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate. The structure of each is represented below:



CLOFIBRATE



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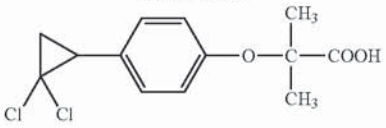
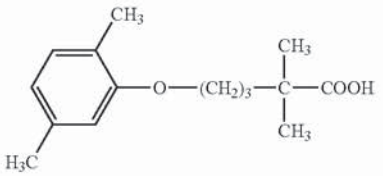
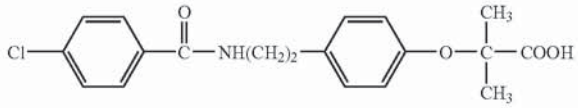


CIPROFIBRATE



GEMFIBROZIL



BENZAFIBRATE

[0026] Fenofibrate is commercially available as Tricor capsules. Each capsule contains 67 mg of micronized fenofibrate. Fenofibrate regulates lipids. Fenofibric acid, the active metabolic of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglyceride-rich lipoprotein (i.e. VLDL). The recommended daily dose of fenofibrate is 67 mg.

[0027] Clofibrate is commercially available as Atromid-S capsules. Each capsule contains 500 mg of clofibrate. Clofibrate lowers elevated serum lipids by reducing the very low-density lipoprotein fraction rich in triglycerides. Serum cholesterol may be decreased. It may inhibit the hepatic release of lipoproteins (particularly VLDL) and potentiate the action of lipoprotein lipase. The recommended daily dose of clofibrate is 2 grams, administered in divided doses.

[0028] Gemfibrozil is commercially available as Lopid tablets. Each tablet contains 600 mg of gemfibrozil. Gemfibrozil is a lipid regulating agent that decreases serum trigylcerides and very low density lipoprotein cholesterol, and increases high density lipoprotein cholesterol. The recommended daily dose of Gemfibrozil is 1200 mg, administered in two divided doses.

[0029] Fibrates include PPAR-alpha agonists which may also act as agonists for PPAR-gamma and/or PPAR-delta subtypes. PPAR-alpha, PPAR-gamma and PPAR-delta agonists may be identified according to an assay described in U.S. Pat. No. 6,008,239, pharmaceutically acceptable salts and esters of PPAR-agonists are likewise included within the scope of this invention.

[0030] Other fibrates may be employed as desired or required. These include, but are not limited to, materials such as bezafibrate and ciprofibrate. The fibrate employed in the composition disclosed herein may be a water-soluble derivative of fenofibrate (2-[4-)4-chlorobenzoyl)phenoxy]-2-methyl-propionic acid-1-methylethyl ester. Fenofibrate is a prodrug that is essentially insoluble in water. Fenofibrate is typically absorbed and then hydrolyzed by tissue and plasma esterases to fenofibric acid, the active metabolite. It is this fenofibric acid that is the active species responsible for pharmacological activity of fenofibrate. Fenofibrate can be employed in connection with the dihydroxy acid salt of a statin or statins. In the broadest embodiment, suitable pharmaceutically acceptable salts of fibric acid shall include, but not be limited to, cationic salts such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and tetramethylammonium, as well as those salts formed from amines, such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N' dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 3-P-chlorobenzyl-2-pyrolidone-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine, and tris(hydroxymethyl)aminomethane, as well as pharmaceutically acceptable esters to include, but not be limited to, C_{1-4}alkyl and C_{1-4}alkyl substituted with phenyl-dimethylamino-N acetylamino groups.

[0031] The effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor alpha (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL-C from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles demonstrate greater affinity for cholesterol receptors and are catabolized rapidly. It is also contemplated that activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II, and HDL-C.

[0032] The therapeutic agent can also be a bile acid sequestrant. Bile acids, the major components of bile, are produced in the liver and are created from cholesterol. Once secreted into the small intestine, the majority of bile acids are reabsorbed and neutralized. The body must then make up for this bile acid loss by manufacturing more, thereby using up more of the cholesterol supplied. Bile acid sequestrants bind bile acids in the intestine, resulting in an interruption of the reabsorption of bile acids thereby reducing the reabsorption efficiency from an amount of approximately 90% to levels lower than this. Nonlimiting examples of available bile acid sequestrants include, but are not limited to, cholestyramine, colestipol, described in U.S. Pat. No. 3,383,281 and colesevelam.

[0033] These and other suitable materials, when orally administered to a mammalian host, form complexes with bile acid conjugates in the intestine and are effective in blocking resorption of bile acids from the intestine. The compound and sequestered bile acids are subsequently excreted from the body in fecal matter thereby increasing the rate at which bile acids are eliminated from the body. Other factors being equal, an increase in the rate at which bile acids are eliminated from the body tends to lower plasma cholesterol level by accelerating the conversion of cholesterol to bile acids in order to maintain a constant supply of bile acids. A portion of the cholesterol for this increased synthesis of bile acids is supplied by removal of cholesterol from the blood plasma.

[0034] Orally administered single compound bile acid sequestrants are typically positively charged resins that bind to negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are

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